Transaminations of Enaminones:
A Synthesis of Tricyclic, N-Aryl, 1,2,3-Triazole-fused Pyridones

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Received November 13, 1989

1-Phenylmethyl- and 1-(4-methoxyphenylmethyl)-5-chloro-1,2,3-triazole-4-carbonyl chlorides acylated the pyrrolidine enamines of cyclopentanone and cyclohexanone, and the resulting enaminones underwent transaminations with aryl amines under acidic conditions. The products then cyclized under basic conditions to linearly fused, tricyclic 3-phenylmethyl- and 3-(4-methoxyphenylmethyl)-4-aryl-8-oxo-4,5,6,7-tetrahydrocyclopenta[b]-1,2,3-triazolo[4,5-e]pyridines, and to 5,6,7,8-tetrahydro-4-aryl-3H-1,2,3-triazolo[4,5-b]quinolin-9(4H)-ones. Similar transaminations afforded the related 8-phenyl- and 8-(3-chlorophenyl)-1,5,7,8-tetrahydro-1-(phenylmethyl)-4H-thieno[3,4-e]-1,2,3-triazolo[4,5-b]pyridin-4-ones. Phase-transfer and catalytic hydrogenolyses of some of these intermediates furnished 4-aryl-8-oxo-4,5,6,7-tetrahydrocyclopenta[b]-1,2,3-triazolo[4,5-e]pyridines and 4-aryl-5,6,7,8-tetrahydro-3H-1,2,3-triazolo[4,5-b]quinoline-9-(4H)-ones.

The 3-(4-methoxyphenylmethyl)-4-aryl intermediates were sterically crowded. Two protons from the methoxyphenylmethylphenylmethylgroups were dramatically shielded because of anisotropic effects exerted by the 4-aryl substituents.

Despite the differing structures of compounds **1** [1], **2** [2], and **3** [3], they have similar neutrophil-dependent anti-inflammatory activities *in vivo* [1,2a,3]. The structural differences suggested that the common pyridine substructures (boldface) of **1-3** influenced the shared biological activities. To substantiate this notion - or to amplify the ac-

tivities - we sought to make pyridones fused to an aromatic, nitrogenous heterocycle other than pyridine. Here we report a synthesis of 1,2,3-triazole-fused pyridones **8.0** and **9.0**. It comprised acylations of enamines **5.0**, transaminations of the resulting enaminones **6.0**, cyclizations of the products **7.0** to **8.0**, and hydrogenolyses of **8.0** to **9.0** (Scheme I).

The choice of triazole-fused pyridones reflected three factors. (1) The triazoles of **8.0** and **9.0** bear a nitrogen atom in the same relative position as the pyridines of **1-3**. (2) Related enaminone transaminations were precedented
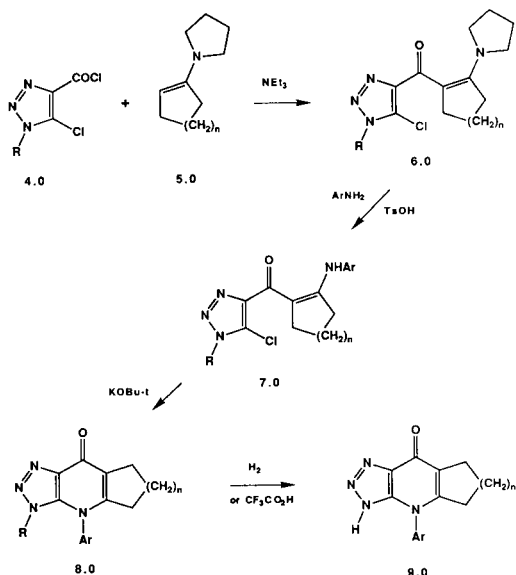
Scheme I

Key to Scheme I

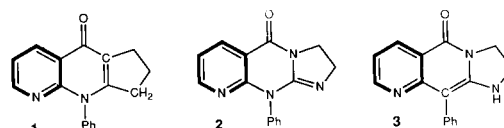| 4.0	5.0	6.0	7.0	8.0	9.0	R [a]	n [a]	Ar [a]
4.1	5.1	6.1	7.1	8.1	9.1	C6H5CH2	1	C6H5
4.1	5.2	6.2	7.2	8.2	9.2	C6H5CH2	2	C6H5
4.1	5.2	6.2	7.3	8.3	9.3	C6H5CH2	2	3-MeO-C6H4
4.2	5.1	6.3	7.4	8.4	9.4	4-MeO-C6H4CH2	1	3-Cl-C6H4
4.2	5.1	6.3	7.5	8.5	9.5	4-MeO-C6H4CH2	1	3-CF3C6H4

[a] As appropriate.

Table I. Inhibitions (%) of RPAR-induced [a] Cellular Influx and Fluid Accumulation in Rat Pleural Cavity

Compound	Polymorphonuclear Neutrophil Influx [b]	Fluid Accumulation [b]	ED50-Values [c, d]	
			Influx	Accumulation
1	82	71	3.9 (1.5-10.0)	8.4 (4.81-15.5)
2	85	57	1.1 (0.4-2.3)	2.2 (0.5-7.7)
3	90	55	3.2 (1.6-6.5)	5.4 (1.8-32.4)
prednisone	25 [e]	44 [e]	[f]	[f]
9.1	0	10	[f]	[f]

[a] RPAR: reversed passive Arthus reaction; see ref [14]. [b] Oral dose of 25 mg/kg. [c] Effective doses are oral and expressed in mg/kg. [d] Parenthetical entries represent the 95% confidence interval. [e] $p \leq 0.01$. [f] ED50-value not determined.

Table II. Inhibitions of RPAR-induced [a] Rat-Paw Edema

Compound	Inhibitions (%, 2-hr.) [b]	ED50-Values [c,d]
1	81	10 (6.1-17.5)
2	84	0.13 [e]
3	92	3.1 (2.0-4.4)
9.1	8	[f]
	0	

[a] RPAR: reversed passive Arthus reaction; see ref [14]. [b] Oral doses of 25 mg/kg. [c] Effective doses are oral and expressed in mg/kg. [d] Parenthetical entries represent the 95% confidence interval. [e] Estimated. [f] Not determined.

[1] and transaminations were thus expected to form **8.0**. (3) Educts **4.0** and **5.0** were readily available.

Pyridones **8.0** and **9.0** lacked antiinflammatory activities at oral doses comparable to those of **1-3**. This finding gave the desired confirmation: *the common pyridine substructures played some (unknown) role in determining the neutrophil-dependent antiinflammatory activities of* **1-3** (Tables I and II).

Acid chlorides **4.1** and **4.2** uneventfully acylated the pyrrolidine enamines (**5.1**, **5.2**) of cyclopentanone and cyclohexanone, forming enaminones **6.1-6.3** (Scheme 1, Table III). Acylations occurred largely or exclusively at carbon; no byproducts of *O*-acylation (enol esters) or *N*-acylation (amides) were isolated. Both kinds of byproducts might have been expected [4]. The unisolated morpholine enaminones corresponding to 1,3-diketones **11** and **13** were unstable. They hydrolysed during (mild) aqueous work-up or silica gel chromatography to **11** and **13** (Scheme II).
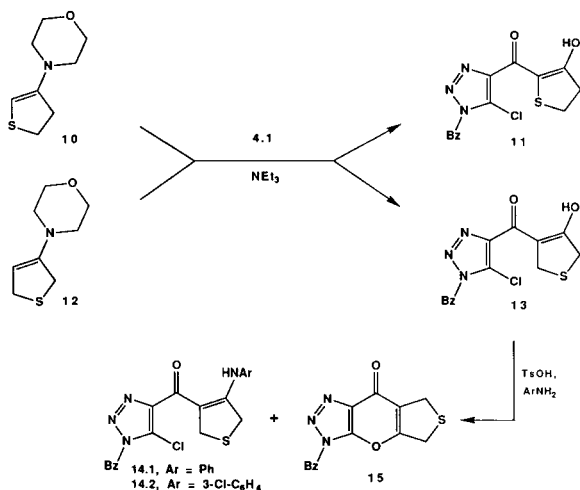
Enaminones **6.1-6.3** underwent the expected transaminations with aniline and with 3-chloro, 3-methoxy-, and 3-trifluoromethylanilines, and furnished enaminones **7.1-7.5** (Scheme I, Table III). Condensations of diketone **13**, with aniline and 3-chloroaniline regioselectively formed the desired enaminones **14.1** (37% (corrected yield)) and **14.2** (37%) (Scheme II). Other components of the mixture containing **14.1** were pyranone **15** (28% (corrected yield)) and educt **13** (54%). By contrast, the isomeric diketone **11** failed (tlc) to react with aniline in the presence of toluenesulfonic acid, conditions that changed **13** to **14.1** and **15** (Scheme III).

Scheme III (Bz = $C_6H_5CH_2$)
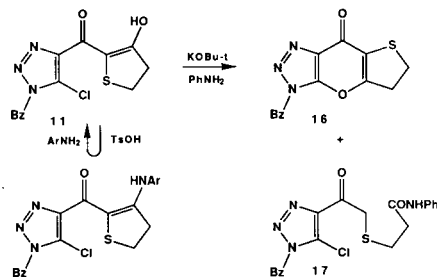
Potassium *t*-butoxide in *t*-butyl alcohol cyclized enaminones **7.1-7.5** to the tricyclic pyridones **8.1-8.5** (Scheme I; Table III). The reagent also converted **14.1** and **14.2** respectively to **18.1** (53%) and **18.2** (27%) (Scheme IV). Byproducts of oxidation **19.1** (21%) and **19.2** (28%) accompanied **18.1** and **18.2**, despite use of a nitrogen atmosphere (Scheme IV). Basic conditions were adopted for cyclizations of **7.0** to **8.0** when only enaminone **7.1** - not pyridone **8.1** - was isolated after treatment of **6.1** with aniline and toluenesulfonic acid. Not surprisingly, basic conditions did not convert diketone **11** to the corresponding pyridone. Compound **11** did undergo ring closure, but to pyranone **16** instead of a pyridone. In the same experiment, diketone **11** formed ketoamide **17** (Scheme III), an expected product of ketone cleavage.

Scheme II (Bz = $C_6H_5CH_2$)

Scheme IV (Bz = $C_6H_5CH_2$)
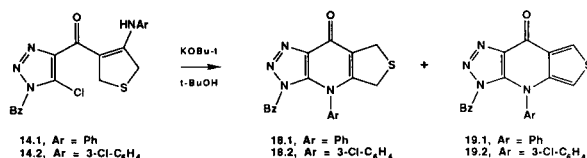
A shielding effect showed that the ring fusions of **8.0** and **9.0** were linear, as expected from the method of synthesis. The resonances of H(2') and (6') of **8.4** and **8.5** lay upfield of those of H(2) and (6) in 4-methoxybenzyl azide, or of those of H(2') and (6') in **7.4** [5]. The Δδ-values (ppm) were -0.8 (**8.4**) and -0.9 (**8.5**) with respect to the azide, and were -0.9 (**8.4**) and -1.0 (**8.5**) with respect to **7.4**. The chemical shifts of H(2') and (6') were remarkably far up-

Table III. Isolated Yields (%) [a]

6.0 → 7.0	7.0 → 8.0	8.0 → 9.0
7.1, 64	8.1, 59	9.1, 68
7.2, 92	8.2, 47	9.2, 51
7.3, 96	8.3, 36	9.3, 54
7.4, 37	8.4, 70	9.4, 50
7.5, 51	8.5, 69	9.5, 75

[a] Conditions and yields were unoptimized and unmaximized, respectively.

field of those of H(3') and (5') in **8.4** and **8.5**. Shielding of H(2') and (6') dominated the expected shielding effect of the methoxyl group on H(3') and (5'). Both assignments of signals to protons followed from a SINEPT experiment which detects three-bond, ¹H to ¹³C couplings [7]. Carried out with compound **8.4**, the experiment showed that H(2') and (6') (δ 6.35 ppm) coupled to the benzyl methylene carbon (δ 52 ppm).

Two aromatic protons of each of **8.1-8.3**, **18.0** and **19.0** were also shielded. Their resonances were presumably those of H(2') and (6'), and the $\Delta\delta$ values were $\geq$ -0.6 ppm compared to the resonance of benzene. No such upfield shifts were apparent in ¹H nmr spectra of compounds **9.1-9.5**, which lacked *N*-benzyl groups while possessing *N*-phenyl groups. Nor were differential shifts evident in spectra of **15** and **16**, which possessed *N*-benzyl groups but lacked *N*-phenyl groups.

Another shielding effect was evident for the diastereotopic benzyl methylene proton of **8.4** and **8.5**. The signal for each fell at δ 4.91 ppm. The resonance was shifted upfield compared to the corresponding signals in **15** and **7.4**. In both cases, the $\Delta\delta$ values (ppm) were -0.8 (*vs.* **15**) and -0.6 (*vs.* **7.4**).

Either of two conformers *e.g.*, **8.4a** and **8.4b** explained both shielding effects as results of anisotropy. In a model of conformer **8.4a**, one of the two diastereotopic benzyl methylene protons lay over the face of the *N*(4) 3-chlorophenyl group (Figure 1a). Also, H(2') of **8.4a** lay under the triazole. In a model of the other conformer **8.4b**, H(2') lay above the triazole face, while the other benzyl methylene proton lay close beneath the *N*(4) 3-chlorophenyl group (Figure 1b).
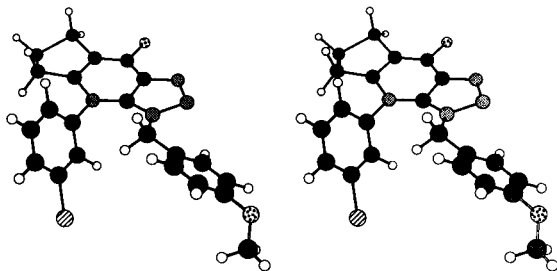
Figure 1a. Stereoscopic View of Conformer [8.4a]

Figure 1b. Stereoscopic View of Conformer [8.4b]

Shielding of one benzyl methylene proton resonance by the N(4) aryl groups confirmed assignments of linear ring fusions. In angularly fused isomers like [**20**], the benzyl and aryl groups would have been too far apart to have accounted for the observed shielding.

Assignments of regiochemistry (**13-18.0**) and ring fusions (**18.0**, **19.0**) followed from a SINEPT experiment with **19.2**. Separate irradiations of the doublet resonances of H(5) (δ 8.4 ppm) and H (7) (δ 6.2 ppm) showed that only H(5) coupled to the carbonyl carbon (C(4), δ 169 ppm). This allowed assignment of the two ¹H signals. The proton H(5) coupled to C(4) over a three-bond path (Figure 2). This established the regiochemistry of **19.2**. No three- or two-bond path connects either thiophene proton of **20** and **21** to their carbonyl carbons. They would have shown no coupling to either proton. A similar SINEPT experiment with pyranone **15** gave a result identical to that with **19.2** (see Experimental). The result confirmed assignment of regiochemical structures to **13** and **14.0**.

Figure 2. Characteristic ³J, ¹³C to ¹H paths (boldface)
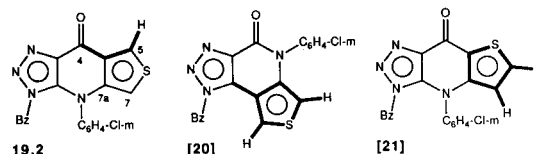
EXPERIMENTAL

Uncorrected melting points were measured on a Thomas-Hoover Capillary Melting Point apparatus or on a MEL-TEMP apparatus. The ir spectra were obtained with Perkin-Elmer 727B or 1320 infrared spectrophotometers, and were recorded with dichloromethane solutions unless otherwise noted. The ν-values are given in cm⁻¹. The uv spectra of the ethanol solutions were determined with a Beckman Model 25 spectrophotometer, and λ max values are in nm. Parenthetical numbers following uv absorptions are logarithmic ϵ values. The ¹H nmr spectra were recorded on Varian EM-390 or XL-200 Supercon instruments; ¹H and ¹³C chemical shifts were determined in deuteriochloroform solutions unless otherwise specified, and are cited in parts per million downfield from tetramethylsilane. Coupling constants are in Hz. SINEPT [7] spectra to determine certain (*vide infra*) three-bond connectivities were recorded on a Varian XL-400 instrument. For these determinations, pulsed polarization transfer *via* long-range ¹H-¹³C couplings was used [7]. Electron-impact mass spectra are reported unless specified otherwise; they were obtained with a Varian CH5 spectrometer. Parenthetical numbers immediately following m/z-values are relative ion intensities in percent. Baker supplied 40 μm silica gel for column chromatography, which was carried out under nitrogen pressure. E. Merck (Darmstadt) provided silica gel F-254 tlc plates; developed plates were visualized in uv light or by spraying with phosphomolybdic acid followed by heating. Organic solutions were routinely dried with magnesium or sodium sulfate after aqueous work-ups.

1-Phenylmethyl-5-chloro-1,2,3-triazole-4-carbonyl Chloride (**4.1**) and 1-(4-Methoxyphenylmethyl)-5-chloro-1,2,3-triazole-4-carbonyl Chloride (**4.2**).

These compounds were made by standard methods. Sodium azide in methanol [8], and in dimethyl formamide [9] respectively, changed benzyl and 4-methoxybenzyl chlorides to the corresponding azides. They condensed with diethyl malonate in ethanol [10] containing potassium *t*-butoxide to give ethyl 1-phenyl-methyl- [10] and 1-(4-methoxyphenylmethyl)-5-hydroxy-1,2,3-triazole-4-carboxylates [9]. To avoid Dimroth rearrangement during crystallization or silica gel chromatography, it was best to use the latter ester as a crude product. Treatment of these 5-hydroxyesters with phosphorous pentachloride [9] (40°, 90 minutes, benzene) gave the corresponding 5-chloro derivatives, which were saponified to the corresponding carboxylic acids [11]. Use of a published procedure [11] converted the carboxylic acids to **4.1** [11] and **4.2**, which were used without purification.

Enamines **5.1**, **5.2**, **10** and **12**.

The Aldrich Chemical Co. supplied 1-(1-pyrrolidinyl)cyclopentene (**5.1**) and 1-(1-pyrrolidinyl)cyclohexane (**5.2**), which were used as received. A mixture of 2,5-dihydro-3-(4-morpholinyl)thiophene (**12**) and 4,5-dihydro-3-(4-morpholinyl)thiophene (**10**) was prepared from 4,5-dihydro-3(2*H*)-thiophenone (Fluka Chemical Corp.) according to a published procedure [12].

[5-Chloro-1-(phenylmethyl)-1*H*-1,2,3-triazol-4-yl][2-(1-pyrrolidinyl)-1-cyclopenten-1-yl]methanone (**6.1**).

Acid chloride **4.1** (11.64 g, 45 mmoles) in dichloromethane (120 ml) was added over 45 minutes to a cold (-40°) solution of distilled enamine **5.1** (6.6 ml, 45 mmoles) and triethylamine (6.3 ml, 45 mmoles) in dichloromethane (120 ml) under nitrogen. When addition was complete, the reaction mixture was allowed to stir 1 hour at -30°. The mixture was then washed with water, 1*M* sodium bicarbonate, and water. The organic solution was dried, filtered, and concentrated. The oily residue (**6.1**, 16 g) was not purified but was used directly in the next step; ir: 1600 (CO), 1500, 1450, 1340; ¹H nmr: 7.35 (s, 5H, *Ar*), 5.45 (s, 2H, CH₂C₆H₅), 3.39 (t, *J* = 6, 4H, 2 CH₂N), 2.86 (t, *J* = 6, CH₂C=C), 2.59 (t, *J* = 6, CH₂C=C), 1.92-1.63 (m, (CH₂)₂ and CH₂); ms: 358 (1, M⁺ for ³⁷Cl), 356 (3, M⁺ for ³⁵Cl), 321 (7, [M - Cl]⁺), 91 (100, [C₇H₇]⁺).

[5-Chloro-1-(phenylmethyl)-1*H*-1,2,3-triazol-4-yl] [2-(1-pyrrolidinyl)-1-cyclohexen-1-yl]methanone (**6.2**).

Enaminone **6.2** was prepared according to the foregoing procedure; the crude product (19 g), which was an oil, was not purified, but was used directly in the next step; ir: 1620 (CO), 1580, 1450, 1330, 1220; ¹H nmr: 7.34 (s, 5H, *Ar*), 5.45 (s, 2H, CH₂C₆H₅), 3.31-3.16 (m, 2H, CH₂), 2.69-2.34 (m, 4H, 2 CH₂), 1.94-1.50 (overlapping m, 10H, 5 CH₂); ms: 370 (0.25, M⁺), 319 (9), 318 (5), 317 (25), 226 (23), 198 (12), 91 (100, [C₇H₇]⁺).

[5-Chloro-1-(4-methoxyphenylmethyl)-1*H*-1,2,3-triazol-4-yl][2-(1-pyrrolidinyl)-1-cyclopenten-1-yl]methanone (**6.3**).

Acid chloride **4.2** (2.03 g, 7.1 mmoles) in dichloromethane (25 ml) was added over 40 minutes to a cold (-78°) solution of enamine **4.1** (1.01 g, 7.36 mmoles) and triethylamine (0.75 g, 7.4 mmoles) in dichloromethane (25 ml) under nitrogen. When addition was complete, the mixture was allowed to stir for 1 hour at -30°. The mixture was then warmed and washed with water; the dried, filtered dichloromethane solution was concentrated. The residue solidified on trituration with ether, giving **6.3** (2.04 g, 74%), as a beige solid, mp 103-107°; ir: 1610 (CO); ¹H nmr (deuteriochloroform, 90 MHz): 7.22 (d, 2H, *J* = 8, Ar*H*(2) and *H*(6), 6.80 (d, 2H, *J* = 8, Ar*H*(3) and *H*(5)), 5.40 (s, 2H, ArCH₂N),

3.63-3.27 (m, 4H, 2 -CH₂N), 2.88 (t, *J* = 7 CH₂C=C), 2.62 (t, *J* = 7.5, -CH₂C=C-), 2.03-1.57 (m, 6H, -(CH₂)₂- and -CH₂-) ms: 386 (2, M⁺ for ³⁵Cl), 164 (1, [C₁₀H₁₄NO]⁺), 136 (3, [C₉H₁₄N]⁺), 121 (100, [MeOC₇H₇]⁺), 107 (1, [MeOC₆H₄]⁺), 70 (47, [C₄H₈N]⁺).

Anal. Calcd. for C₂₀H₂₃ClN₄O₂: C, 62.09; H, 5.99; Cl, 9.16; N, 14.48. Found: C, 61.31; H, 6.01; Cl, 9.19; N, 14.19. No acceptable value for C was obtained.

[2-Arylamino-1-cyclopenten-1-yl]- and [2-Arylamino-1-cyclohexen-1-yl][5-chloro-1-(arylmethyl)-1*H*-1,2,3-triazol-4-yl]methanones **7.1-7.5** from Enaminones **6.1-6.5**.

These compounds were prepared according to the following procedure. A mixture of enaminone **6.0** (50 mmoles), aromatic amine (50 mmoles), and anhydrous *p*-toluenesulfonic acid (prepared from the monohydrate (50 mmoles) by azeotropic distillation) in benzene (300 ml) was refluxed 18 hours under a Dean-Stark trap in nitrogen. Benzene was removed, and a solution of the residue in dichloromethane was washed with 1*M* sodium bicarbonate, water, 1*N* hydrochloric acid, and with water. The organic solution was dried, filtered, and concentrated. The crude products were purified by crystallization or chromatography.

[2-(Phenylamino)-1-cyclopenten-1-yl][5-chloro-1-(phenylmethyl)-1*H*-1,2,3-triazol-4-yl]methanone (**7.1**).

Dichloromethane eluted compound **7.1** (1.3 g, 67%) from silica gel, and crystallization from acetonitrile-carbon tetrachloride gave a pure sample as yellow crystals, mp 121-123°; ir: 1600 (CO), 1540, 1500, 1450, 1340, 1200, 1060, 1030; ¹H nmr: 12.32 (br s, 1H, N*H*), 7.70-6.87 (m, 5H, *Ar*), 7.39 (s, 5H, CH₂C₆H₅), 5.57 (s, 2H, -CH₂C₆H₅), 3.20 (t, *J* = 6, 2H, -CH₂-), 2.82 (t, *J* = 6, 2H, -CH₂-), 1.94 (quintet, J = 6, 2H, -CH₂); ms: 380 (6, M⁺ for ³⁷Cl), 378 (21, M⁺ for ³⁵Cl), 91 (100, [C₇H₇]⁺).

Anal. Calcd. for C₂₁H₁₉ClN₄O: C, 66.58; H, 5.06; Cl, 9.36; N, 14.79. Found: C, 66.14; H, 4.89; Cl, 9.40; N, 14.61.

[2-(Phenylamino)-1-cyclohexen-1-yl][5-chloro-1-(phenylmethyl)-1*H*-1,2,3-triazol-4-yl]methanone (**7.2**).

Crude solid **7.2** (5.2 g, 50%) was eluted by dichloromethane from silica gel; ir: 1610 (CO), 1570, 1540, 1500, 1340, 1230, 1140; ¹H nmr: 13.56 (br s, 1H, N*H*), 7.63-6.91 (m, 5H, *Ar*), 7.33 (s, 5H, -C₆H₅), 5.50 (s, 2H, -CH₂-), 2.75 (br t, 2H, -CH₂), 2.42 (br t, 2H, -CH₂-), 1.66-1.50 (m, 4H, -(CH₂)₂-); ms: 394 (5, M⁺ for ³⁷Cl), 392 (12, M⁺ for ³⁵Cl), 329 (28), 91 (100, [C₇H₇]⁺).

[2-(3-Methoxylphenylamino)-1-cyclohexen-1-yl][5-chloro-1-(phenylmethyl)-1*H*-1,2,3-triazol-4-yl]methanone (**7.3**).

Dichloromethane-ethyl acetate (9:1 by volume) eluted enaminone **7.3** (5.24 g, 47%) from silica gel; the material, which was an oil, was not purified, but was used directly in the next step, ir: 1620 (CO), 1570, 1490, 1450, 1340, 1230, 1150, 1040; ¹H nmr: 13.60 (br s, 1H, N*H*), 8.72-6.69 (m, 3H, *Ar*), 6.33-6.20 (m, 1H, *Ar*), 7.38 (s, 5H, -CH₂C₆H₅), 5.5 (s, 2H, -CH₂N), 3.76 (s, 3H, -OCH₃), 2.90-2.75 (m, 2H, -CH₂-), 2.57-2.42 (m, 2H, -CH₂-), 1.75-1.55 (m, 4H, 2 -CH₂); ms: 424 (1, M⁺ for ³⁷Cl), 422 (2, M⁺ for ³⁵Cl), 359 (3), 123 (27), 91 (100, [C₇H₇]⁺).

[2-(3-Chlorophenylamino)-1-cyclopenten-1-yl][5-chloro-1-(4-methoxyphenylmethyl)-1*H*-1,2,3-triazol-4-yl]methanone (**7.4**).

Dichloromethane eluted compound **7.4** from silica gel, and the product (mp 135.5-137.5°) crystallized from 2-propyl acetate in a

yield of 40% (from 4.7 mmoles of **6.3**); ir: 1610 (CO), 1590; ^{1}H nmr: (200 MHz) 12.28 (br s, N*H*), 7.34-6.97 (m, *Ar*), 6.87 (d, *J* = 7.5, 2H, 2 C*H ortho* to MeO-), 5.50 (s, 2H, - C*H$_2$*N), 3.80 (s, 3H, C*H$_3$*O-), 3.17 (t, 2H, *J* = 7.5, -C*H$_2$*C=C), 2.85 (t, 2H, *J* = 7.8, -C*H$_2$*C=C), 2.07-1.89 (m, 2H, -C*H$_2$*-); ^{13}C nmr: (75.4 MHz) 179 (*C*O), 166 (N*C*Cl), 160 (MeO*C*), 142 (CH$_2$*C*NH), 141 (*ipso* NH*C*$_6$H$_4$-), 135 (=*C*-Cl), 130 (Ar), 129 (*ortho* -CH$_2$*C*$_6$H$_4$-), 127 (*ipso* CH$_2$*C*$_6$H$_4$- or *C*CH$_2$N), 125 (N*C*CO), 125 (Ar), 122 (Ar), 120 (Ar), 114 (*ortho* MeO*C*H$_4$-), 109 (CH$_2$*C*CO-), 55 (-O*C*H$_3$), 51 (Ar*C*H$_2$N), 33 (=C*C*H$_2$-), 31 (=C*C*H$_2$), 23 (-*C*H$_2$-); ms: 446 (1, M$^+$ for ^{37}Cl$_2$), 444 (6, M$^+$ for ^{37}Cl^{35}Cl), 442 (9, M$^+$ for ^{35}Cl$_2$), 321 (12, [M -CH$_3$OC$_7$H$_6$]$^+$), 222 (2, [C$_{12}$H$_{11}$ ^{37}ClNO]$^+$), 220 (4, [C$_{12}$H$_{11}$^{35}ClNO]$^+$), 192 (1, [C$_{11}$H$_{11}$^{35}ClN]$^+$), 121 (100, [CH$_3$OC$_7$H$_6$]$^+$), 113 (2, [C$_6$H$_4$^{37}Cl]$^+$), 111 (6, [C$_6$H$_4$^{35}Cl]$^+$).

Anal. Calcd. for C$_{22}$H$_{20}$Cl$_2$N$_4$O$_2$: C, 59.60; H, 4.55; Cl, 16.00; N, 12.64. Found: C, 59.69; H, 4.49; Cl, 4.82; N, 12.57. No acceptable microanalysis of chlorine was obtained.

[2-(3-Trifluoromethylphenylamino)-1-cyclopenten-1-cyclopenten-1-yl][5-chloro-1-(4-methoxyphenylmethyl)-1*H*-1,2,3-triazol-4-yl]methanone (**7.5**).

Compound **7.5**, mp 147.5-150°, which was obtained in a yield of 51% (from 14.1 mmoles of **6.3**) crystallized from 2-propyl acetate; ir: 1600, 1330; ^{1}H nmr: (200 MHz) 12.40 (s, N*H*), 7.53-7.24 (m, *Ar*), 6.87 (d, *J* = 7.5, 2H, 2 C*H ortho* to MeO-), 5.50 (s, 2H, Ar-C*H$_2$*N), 3.80 (s, 3H, C*H$_3$*O-), 3.21 (t, J = 7.5, 2H, C=CC*H$_2$*-), 2.89 (t, *J* = 7.5, 2H, C=CC*H$_2$*-), 2.06-1.87 (m, *J* = 7.5, 2H, -C*H$_2$*-); ^{13}C nmr: (75.4 MHz) 180 (*C*O), 166 (*C*Cl), 160 (MeO*C*), 142 (-CH$_2$*C*NH), 140 (*ipso* *C*NH), 131 (q, $^2J_{C-F}$ = 31.2, *C*CF$_3$), 130 (*Ar*), 129 (2 *C*H *ortho* to MeO-), 128 (*ipso* *C*CH$_2$-), 125 (N*C*CO), 124 (*Ar*), 121, (*Ar*) 118, (*Ar*) 114 (2 *C*H *ortho* to MeO-), 110 (CH$_2$*C*CO-), 55 (*C*H$_3$O-), 51 (-*C*H$_2$N-), 33 (C=C*C*H$_2$-), 30 (C=C*C*H$_2$-), 23 (-*C*H$_2$-); ms: 478 (2, M$^+$ for ^{37}Cl), 476 (6, M$^+$ for ^{35}Cl), 355 (9, [M -MeOC$_7$H$_6$]$^+$), 254 (2, [C$_{13}$H$_{11}$F$_3$NO]$^+$), 160 (5, [C$_7$H$_5$F$_3$N]$^+$), 145 (3, [C$_7$H$_4$F$_3$]$^+$), 121 (100, [MeOC$_7$H$_6$]$^+$), 69 (7,[CF$_3$]$^+$).

Anal. Calcd. for C$_{23}$H$_{20}$ClF$_3$N$_4$O$_2$: C, 57.93; H, 4.23; Cl, 7.44; F, 11.96; N, 11.75. Found: C, 57.86; H, 4.24; Cl, 7.47; F, 11.82; N, 11.76.

3-Phenylmethyl-4-phenyl-8-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]-1,2,3-triazolo[4,5-*e*]pyridine (**8.1**).

A mixture of **7.1** (11.15 g, 29 mmoles) and potassium *t*-butoxide (4.2 g, 36 mmoles) in *t*-butyl alcohol (400 ml) was stirred at 25° for 20 hours under nitrogen. The resulting precipitate was collected by filtration and the filtrate was concentrated; precipitate and residue were combined and partitioned between water and dichloromethane. The organic solution was dried, filtered, and concentrated. Dichloromethane-ethyl acetate (1:1 by volume) eluted **8.1** from silica gel, and the product crystallized from ethyl acetate-dichloromethane to give a pure sample of **8.1** (5.9 g, 59%), mp 241-242°; ir: 1620 (CO), 1590, 1550, 1490, 1360, 1340, 1310; uv: 225 (4.20), 256 (3.90), 293 (4.17); ^{1}H nmr: 7.58-7.05 (m, 8H, -C$_6$H$_5$ and CH$_2$C$_6$H$_5$), 6.48-6.32 (m, 2H, *H* (2') and H(6')), 5.10 (s, 2H, -C*H$_2$*C$_6$H$_5$), 2.88 (t, *J* = 7.5, 2H, -C*H$_2$*CCO-), 2.50 (t, *J* = 7.5, 2H, -C*H$_2$*CCN-), 2.18-1.92 (m, 2H, -CH$_2$C*H$_2$*CH$_2$-); ^{13}C nmr: (400 MHz) 170 (*C*O), 153 (*C* (4a)), 140 (*C*(3a), 136 (*C*(8a)), 135 (*Ar*), 130.4 (*Ar*), 129.8 (*Ar*), 129.7 (*Ar*), 128.6 (*Ar*), 128.5 (*Ar*), 127.9 (*Ar*), and 126 (*Ar*), 125 (*C*(7a)), 52 (-*C*H$_2$C$_6$H$_5$), 33 (*C*(5)*), 28 (*C*(7)*), 22 (*C*(6)); CI-ms: (methanol) 344 (25, [M + 2]$^+$), 343 (100, [M + 1]$^+$), 341 (21), 314 (21), 314 (10, [M - N$_2$]$^+$).

Anal. Calcd. for C$_{21}$H$_{18}$N$_4$O: C, 73.66; H, 5.30; N, 16.36. Found: C, 73.69; H, 5.05; N, 16.42.

5,6,7,8-Tetrahydro-4-phenyl-3-(phenylmethyl)-3*H*-1,2,3-triazolo-[4,5-*b*]quinolin-9(4*H*)-one (**8.2**).

A mixture of **7.2** (8.79 g, 22 mmoles) and potassium *t*-butoxide (3.2 g, 28.5 mmoles) in *t*-butyl alcohol (300 ml) was stirred under nitrogen for 24 hours at 25°. The reaction mixture was then worked up as described above for compound **8.1**. The crude product cyrstallized after trituration with ethyl acetate; recrystallization from ethyl acetate-dichloromethane gave pure **8.2** (3.7 g, 47%), mp 241-242°; ir: 1620 (CO), 1590, 1550, 1490, 1360-1340, 1300; uv: 230 (4.13), 294 (4.22); ^{1}H nmr: 7.60-7.00 (m, 8H, -C$_6$H$_5$ and -CH$_2$C$_6$H$_5$), 6.44-6.32 (m, 2H, *H*(2') and *H*(6')), 4.94 (s, 2H, -C*H$_2$*C$_6$H$_5$), 2.60 (br s, 2H, -C*H$_2$*-), 2.03 (br s, 2H, -C*H$_2$*-), 1.63 (m, 4H, (-C*H$_2$*)$_2$-); ^{13}C nmr: (400 MHz) 172 (*C*O), 146 (*C*(4a)), 139 (*C*(3a)), 135.5 (*C* (9a)), 135.3 (*Ar*), 134 (*Ar*), 131, 129.9, 129.7, 128.3, 127.7, and 125.6 (*Ar*), 122 (*C* (8a)), 52 (-*C*H$_2$C$_6$H$_5$), 28, 22.4, 22.3, and 21 (C (5-8)); ms: 356 (31, M$^+$), 328 (15), 327 (45), 91 (100, [C$_7$H$_7$]$^+$).

Anal. Calcd. for C$_{22}$H$_{20}$N$_4$O: C, 74.13; H, 5.65; N, 15.72. Found: C, 73.80; H, 5.54; N, 15.75.

5,6,7,8-Tetrahydro-4-(3-methoxyphenyl)-3-(phenylmethyl)-3*H*-1,2,3-triazolo[4,5-*b*]quinolin-9(4*H*)-one (**8.3**).

A mixture of **7.3** (8.79 g, 20.8 mmoles) and potassium *t*-butoxide (3.1 g, 27.6 mmoles) in *t*-butyl alcohol (300 ml) was stirred at 25° under nitrogen for 14.5 hours. After work-up (as described above for **8.1**) and trituration with ethyl acetate, the residue crystallized. Recrystallization from dichloromethane-ethyl acetate gave pure **8.3** (2.91 g, 36%), mp 243-245°; ir: 1620 (CO), 1600, 1590, 1550, 1490, 1240, 1040; ^{1}H nmr 7.40-7.00 (m, 5H, -CH$_2$C$_6$H$_5$), 6.90-6.70 (m, 2H, *H*(3') and *H*(5')), 6.56-6.36 (m, 2H, *H*(2') and *H*(6')), 5.05 and 4.85 (AB q, J_{AB} = 15 Hz 2H, -C*H$_2$*C$_6$H$_5$), 3.70 (s, 3H, -OC*H$_3$*), 2.63 (br s, 2H, -C*H$_2$*), 2.15 (br s, 2H, -C*H$_2$*-), 1.79-1.55 (m, 4H, -(CH$_2$)$_2$-); ms: 386 (15, M$^+$), 357 (100, [M - 29]$^+$).

Anal. Calcd. for C$_{23}$H$_{22}$N$_4$O$_2$: C, 71.48; H, 5.74; N, 14.50. Found: C, 71.10; H, 5.66; N, 14.73.

3-(4-Methoxyphenylmethyl)-4-(3-chlorophenyl)-8-oxo-4,5,6,7-tetra-hydrocyclopenta[*b*]-1,2,3-triazolo[4,5-*e*]pyridine (**8.4**).

Enaminone **7.4** (1.1 g, 2.4 mmoles) was stirred 3 days with potassium *t*-butoxide (0.34 g, 3.0 mmoles) in *t*-butyl alcohol (30 ml) at ambient temperature. A precipitate was apparent after 15 minutes. The mixture was diluted with dichloromethane, filtered through diatomaceous earth, and was concentrated to give a colorless solid. Crystallization from ethanol-dichloromethane provide **8.4** (0.68 g, 70%) as a colorless solid, mp 250.5-253.0°; ir: 1630 (CO); ^{1}H nmr: (200 mHz) 8.75-7.35 (m, 3H, *Ar*), 7.00 (t, 1H, NCC*H*CCl), 6.70 (d, 2H, *J*(3'-2') = *J*(5'-6') = 10 Hz, *H*(3') and *H*(5')), 6.35 (d, 2H, *J*(3'-2') = *J*(5'-6') = 10 Hz, *H*(2') and *H*(6')), 5.33 (d, 1H, J_{AB} = 16 Hz, ArC*H$_2$*N), 4.91 (d, 1H, J_{AB} = 16 Hz, Ar-C*H$_2$*N), 3.78 (s, 3H, -OC*H$_3$*), 2.88 (t, 2H, *J*(7*-6) = 7.5 Hz, *H* (7)*), 2.49 (t, 2H, *J*(5*-6) = 7.5 Hz, *H*(5)*), 2.14-1.95 (m, 2H, *H*(6)); ^{13}C nmr: (75.4 MHz) 170 (*C*O), 159 (MeO*C*), 152 (*C*(3a)), 139 (*C*(4a)*), 137 (*C*(8a)*), 136 (*C*Cl), 135 (*C*(1'')), 130.88 (*C*(5'')**), 130.84 (*C*(6'')**), 129 (*C*(2'')), 127.2 (*C*(4'')), 126.9 (*C*(2') and (6')), 126.4 (*C*(7a)), 125.7 (*C*(NCH$_2$*C*)), 114 (*C*(3') and *C*(5')), 55 (-O*C*H$_3$), 52 (Ar*C*H$_2$N), 33 (*C*(5)†), 28 (*C*(7)†), 22 (*C*(6)); ms: 408 (6, M$^+$ for ^{37}Cl), 406 (18, M$^+$ for ^{35}Cl), 380 (5, [M-N$_2$]$^+$ for ^{37}Cl), 378 (14, [M-N$_2$]$^+$ for ^{35}Cl), 121 (100, [C$_8$H$_9$O]$^+$), 113 (2, [C$_6$H$_4$^{37}Cl]$^+$), 111 (8, [C$_6$H$_4$^{35}Cl]$^+$).

According to SINEPT experiments [7], the *H*(2') and *H*(6') resonances (δ 6.35 ppm) coupled to the ArC*H$_2$*N resonance (δ 52

ppm). The $H(3')$ and $H(5')$ resonances (δ 6.70 ppm) did not. The ArCH$_2$N resonance was distinguished from the -OCH$_3$ resonance (δ 55 ppm) by an attached proton test.

Anal. Calcd. for $C_{22}H_{19}ClN_4O_2$: C, 64.94; H, 4.71; Cl, 8.71; N, 13.77. Found: C, 64.76; H, 4.66; Cl, 8.78; N, 13.82.

3-(4-Methoxyphenylmethyl)-4-(3-trifluoromethylphenyl)-8-oxo-4,5,6,7-tetrahydrocyclopenta[b]-1,2,3-triazolo[4,5-e]pyridine (8.5).

Enaminone **7.5** (3.3 g, 6.9 mmoles) was stirred with potassium *t*-butoxide (0.8 g, 7 mmoles) in *t*-butyl alcohol (100 ml) at ambient temperature for 4 days. The mixture was diluted with dichloromethane, filtered through diatomaceous earth, and was concentrated to give a colorless solid. Recrystallization of the solid from acetonitrile provided **8.5** (2.09 g, 69%), mp 280-283°; ir: 1630 (CO); ^{1}H nmr: 7.87-7.62 (m, 4H, *Ar*), 6.65 (d, 2H, $J(3'-2') = J(5'-6') = 10$ Hz, $H(3')$ and $H(2')$), 6.27 (d, 2H, $J(2'-3') = J(6'-5') = 10$ Hz, $H(2')$ and $H(6')$), 5.31 (d, 1H, $J_{AB} = 16$ Hz, ArCH$_2$N), 4.91 (d, 1H, $J_{AB} = 16$ Hz ArCH$_2$N), 3.72 (s, 3H, -OCH$_3$), 2.90 (t, 2H, $J(7-6) = 7.5$ Hz, $H(7')$), 2.45 (d of t, 2H, $J(5-6) = 7.5$ Hz, $J = 3$ Hz, H $(7')$), 2.15-1.95 (m, 2H, $H(6)$); ms: 440 (11, M$^+$), 412 (12, [M - N$_2$]$^+$), 145 (6, [C$_6$H$_4$CF$_3$]$^+$), 121 (100, [C$_7$H$_6$OMe]$^+$).

Anal. Calcd. for $C_{23}H_{19}F_3N_4O_2$: C, 62.72; H, 4.35; F, 12.94; N, 12.72. Found: C, 62.44; H, 4.22; F, 12.59; N, 12.63.

4-Phenyl-8-oxo-4,5,6,7-tetrhydrocyclopenta[b]-1,2,3-triazolo-[4,5-e]pyridine (9.1).

Catalytic transfer hydrogenolysis according to a published procedure [13] gave **9.1**. A mixture of **8.1** (4.1 g, 12 mmoles), methanol (620 ml), acetic acid (40 ml), 10% palladium-on-carbon (2 g), and ammonium formate (6 g) was stirred under nitrogen at 25° for 18 hours. Following filtration, concentration, and trituration with water, recrystallization from methanol gave **9.1** (1.75, 58%) as colorless crystals, mp 312-314°; ir: (mineral oil): 2700-2500 br, 1610, 1590, 1540, 1490, 1420, 1340, 1290, 1190, 1160; uv: 254 (3.87), 310 (4.23); ^{1}H nmr (perdeuteriodimethyl sulfoxide): 7.61 (s, 5H, *Ar*), 6.00 (br s, 1H, N*H*), 2.76 (t, $J = 7.5$ Hz, 4H, $H(5)$ and H (7)), 2.02 (m, $J = 7.5$ Hz, 2H, H (6)); ms: 254 (2), 253 (16, [M + 1]$^+$), 252 (92, M$^+$), 251 (30), 224 (100, [M - 28]$^+$).

Anal. Calcd. for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.49; H, 4.77; N, 22.28.

Catalytic hydrogenolysis of **8.1** in methanol under 50 psi of hydrogen at 80° for 3 hours also gave **9.1** (48%), which was identified by comparison of ^{1}H nmr and ir spectra with those of an authentic sample and by mixed melting point determination.

5,6,7,8-Tetrahydro-4-phenyl-3H-1,2,3-triazolo[4,5-b]quinolin-9(4H)-one (9.2).

A mixture of **8.2** (1.8 g, 5.0 mmoles), methanol (500 ml), acetic acid (50 ml), 10% palladium-on-carbon (1 g), and ammonium formate (1.6 g, 25 mmoles) was stirred under nitrogen at 25° for 6 hours [13]. Another portion of ammonium formate (2.6 g, 41 mmoles) in methanol (100 ml) was added, and the resulting mixture was stirred for a further 15 hours. Following filtration, concentration, and trituration with water, recrystallization from methanol gave **9.2** (0.84 g, 51%) as colorless crystals, mp 325-325.5°; ir: (mineral oil): 2760-2400 br (NH), 1620, 1590, 1540, 1480, 1300, 1160; uv 259 (3.92), 309 (4.26); ^{1}H nmr (deuteriochloroform-perdeuteriodimethyl sulfoxide): 7.66-7.36 (m, 5H, *Ar*), 7.59 (br s, 1H, N*H*) 2.59 (br s, 2H, -CH$_2$-), 2.35 (br s, 2H, -CH$_2$), 1.69 (br s, 4H, -(CH$_2$)$_2$-); ms: 267 (12, [M + 1]$^+$), 266 (64, M$^+$), 2.38 (67), 210 (100).

Anal. Calcd. for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found:

C, 67.66; H, 5.15; N, 21.02.

5,6,7,8-Tetrahydro-4-(3-methoxyphenyl)-3H-1,2,3-triazolo[4,5--b]quinolin-9(4H)-one (9.3).

A mixture of **8.3** (2.0 g, 5.2 mmoles), methanol (450 ml), acetic acid (60 ml), 10% palladium-on-carbon (1 g), and ammonium formate (1.7 g) was stirred under nitrogen at 25° [13]. Two more portions of ammonium formate (1.7 g) in methanol (100 ml) were added at intervals of 20 hours; the total reaction time was 80 hours. Following filtration, concentration, and trituration with water, recrystallization from methanol gave **9.3** (0.83 g, 54%), mp 301-302°; ir: (mineral oil): 3100-2300, 1620, 1600, 1540, 1480, 1310, 1280, 1240, 1210, 1150, 1090, 1040, 1000, 780; ^{1}H nmr (deuteriochloroform-perdeuteriodimethyl sulfoxide): 7.49 (t, $J = 7.5$ Hz, 1H, $H(2')$), 7.14-6.89 (m, 3H, *Ar*), 6.50 (br s, 1H, N*H*), 3.84 (s, 3H, -OCH$_3$), 2.64 (br s, 2H, -CH$_2$-) overlapping with 2.40 (br s, 2H, -CH$_2$-), 1.70 (br s, 4H, -(CH$_2$)$_2$-); ms: 297 (18, [M + 1]$^+$), 296 (90, M$^+$), 295 (18, [M - 1]$^+$), 240 (100).

Anal. Calcd. for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.90. Found: C, 64.71; H, 5.36; N, 19.03.

4-(3-Chlorophenyl)-8-oxo-4,5,6,7-tetrahydrocyclopenta[b]-1,2,3-triazolo[4,5-e]pyridine (9.4).

Protected triazole **8.4** (0.600 g, 1.47 mmoles) was stirred in trifluoroacetic acid (15 ml) at 65° under nitrogen for 4 hours. The trifluoroacetic acid was evaporated and the residue triturated in ether. The resulting solid, mp 290-292° (dec from 280°), was recrystallized from acetonitrile to give **9.4** (0.212 g, 50%) as colorless crystals, mp 280°; ir: 3200-2000 br, 1610 (CO), 1460; ^{1}H nmr (200 MHz, perdeuteriodimethyl sulfoxide): 7.80 (s, 1H, NC-C*H*CCl), 7.70-7.55 (m, 3H, *Ar*), 3.8-3.0 (br s, N*H*), 2.89-2.71 (m, 4H, $H(5)$ and $H(7)$) 2.14-1.95 (m, 2H, $H(6)$); ms: 288 (16, M$^+$ for ^{37}Cl), 286 (51, M$^+$ for ^{35}Cl), 260 (32, [M - N$_2$]$^+$), 258 (100, [M - N$_2$]$^+$ for ^{35}Cl), 223 (61, [M - N$_2$ - Cl]$^+$), 113 (20, [C$_6$H$_4$^{37}Cl]$^+$), 111 (61, [C$_6$H$_4$^{35}Cl]$^+$).

Anal. Calcd. for $C_{14}H_{11}ClN_4O$: C, 58.65; H, 3.87; Cl, 12.37; N, 19.54. Found: C, 58.99; H, 3.97; Cl, 12.58; N, 19.53.

4-(3-Trifluoromethylphenyl)-8-oxo-4,5,6,7-tetrahydrocyclopenta-[b]-1,2,3-triazolo[4,5-e]pyridine (9.5).

Protected triazole **8.5** (1.82 g, 4.13 mmoles) was stirred in trifluoroacetic acid (40 ml) at 65° under nitrogen for 5 hours. The trifluoroacetic acid was evaporated and the residue was triturated in ether. Recrystallization of the resulting solid from acetonitrile in a Soxhlet extractor provided compound **9.5** (0.996 g, 75%), mp 300-301.5°; ir: (mineral oil): 3200-2100 br NH), 1640 (CO), 1460; ^{1}H nmr: 8.10 (s, 1H, $H(2')$), 8.05-7.79 (m, 3H, *Ar*), 3.35 (br s, N*H*), 2.76 (t, 4H, $J(5-6) = J(7-6) = 7.5$ Hz, H (5) and H (7)), 2.15-1.91 (m, 2H, $H(6)$); ms: 321 (15, [M + 1]$^+$), 320 (77, M$^+$), 319 (26, [M - 1]$^+$), 292 (100, [M - N$_2$]$^+$), 251 (2, [M - CF$_3$]$^+$), 223 (14, [M -N$_2$ - CF$_3$]$^+$), 145 (18, [C$_6$H$_4$CF$_3$]$^+$).

Anal. Calcd. for $C_{15}H_{11}F_3N_4O$: C, 56.25; H, 3.46; F, 17.80; N, 17.49. Found: C, 56.43; H, 3.52; F, 17.24; N, 17.50. No acceptable microanalysis for fluorine was obtained. Exact mass: Calcd. m/e; 321.0963; Found, 321.0959.

[5-Chloro-1-(phenylmethyl)-1H-1,2,3-triazol-4-yl](4,5-dihydro-3-hydroxy-2-thienyl)methanone (11).

Acid chloride **4.1** (20.9 g, 81.8 mmoles) in dichloromethane (60 ml) was added to a cold (-30°) dichloromethane solution (50 ml) of a mixture (14 g, 82 mmoles) of enamines **10** and **14** [12] and triethylamine (8.35 g, 82 mmoles). The reaction mixture was stir-

red 1 hour at -30° and overnight at 25°. The solution was then washed with water, dried, and concentrated. The residue was a mixture of two major products, **11** and **13**, which chromatography over silica gel separated. Dichloromethane-hexanes (70:30 by volume) then eluted compound **11** (4.5 g, 17%, yellow crystals, mp 118-120° from ether) from silica gel as the less mobile product; ir: 3050-2920 (OH), 1640 (CO), 1610, 1500, 1460-1420, 1380, 1290-1260, 1200, 1180, 1140, 1010; ¹H nmr: 13.53 (br s, 1H, N*H*), 7.36 (s, 5H, -C₆*H*₅), 5.55 (s, 2H, -C*H*₂C₆H₅), 3.23-3.03 (m, 2H, -C*H*₂-), 2.93-2.73 (m, 2H, -C*H*₂-); ms: 323 (4, M⁺ for ³⁷Cl), 321 (10, M⁺ for ³⁵Cl), 230 (1, [M - C₇H₇]⁺), 91 (100, [C₇H₇]⁺).

Anal. Calcd. for C₁₄H₁₂ClN₃O₂S: C, 52.25; H, 3.76; Cl, 11.02; N, 13.06; S, 9.96. Found: C, 52.12; H, 3.81; Cl, 10.89; N, 13.01; S, 9.99.

[5-Chloro-1-(phenylmethyl)-1*H*-1,2,3-triazol-4-yl](2,5-dihydro-4-hydroxy-3-thienyl)methanone (13).

Compound **13** (4.5 g, 17%, colorless crystals, mp 110-113° from ether) was prepared as described for **11**, and was isolated by chromatography as the more mobile product; ir: 3030-2900 (OH), 1600 (CO), 1460, 1320, 1220, 1050, 860; ¹H nmr: 14.99 (br s, 1H, N*H*), 7.36 (s, 5H, -C₆*H*₅), 5.55 (s, 2H, -C*H*₂C₆H₅), 4.26 (s, 2H, -C*H*₂-), 3.67 (s, 2H, -C*H*₂-); ms: 323 (5, M⁺ for ³⁷Cl), 321 (13, M⁺ for ³⁵Cl), 230 (15, [M - C₇H₇]⁺), 91 (100, [C₇H₇]⁺).

Anal. Calcd. for C₁₄H₁₂ClN₃O₂S: C, 52.25; H, 3.76; Cl, 11.02; N, 13.06; S, 9.96. Found: C, 52.24; H, 3.80; Cl, 10.90; N, 13.00; S, 10.10.

[5-Chloro-1-(phenylmethyl)-1*H*-1,2,3-triazol-4-yl](2,5-dihydro-4-(phenylamino)-3-thienyl]methanone (14.1).

A mixture of compound **13** (9.0 g, 28 mmoles), *p*-toluenesulfonic acid monohydrate (5.3 g, 28 mmoles), aniline (2.6 g, 28 mmoles), and benzene (240 ml) was refluxed 30 hours under a Dean-Stark trap in nitrogen. The cooled reaction mixture was diluted with dichloromethane and the solution was washed with 1*M* sodium bicarbonate solution and with water. The organic solution was dried, filtered, and concentrated. The residue (12 g), which was a mixture of **13**, **14.1**, and **15**, was chromatographed. Elution of the column with dichloromethane-ethyl acetate (1:1 by volume) furnished starting material (**13**, 4.9 g, 54% recovery, identified by tlc, mixed mp, and ¹H nmr spectroscopy) as the most mobile component. Compound **14.1** (1.9 g, 38% yield (corrected), mp 157-157.5° from petroleum ether) was eluted next. Finally, compound **15** (*vide infra*) was eluted; ir: 3050 (NH), 1610 (CO), 1600, 1550, 1240, 1160, 1040, 870; ¹H nmr: 12.52 (br s, 1H, N*H*), 7.40 (s, 5H, *Ar*), 7.40-7.15 (overlapping m, 5H, *Ar*), 5.52 (s, 2H, -C*H*₂C₆H₅), 4.50 (t, *J* = 3 Hz, 2H, -C*H*₂-), 3.98 (t, *J* = 3, -C*H*₂-); ms: 398 (12, M⁺ for ³⁷Cl), 396 (31, M⁺ for ³⁵Cl), 91 (100, [C₇H₇]⁺).

Anal. Calcd. for C₂₀H₁₇ClN₄OS: C, 60.52; H, 4.32; Cl, 8.92; N, 14.12; S, 8.07. Found: C, 60.22; H, 4.34; Cl, 9.15; N, 14.05; S, 8.22.

[5-Chloro-1-(phenylmethyl)-1*H*-1,2,3-triazol-4-yl](2,5-dihydro-4-(3-chlorophenylamino)-3-thienyl]methanone (14.2).

A mixture of **13** (4.48 g, 13.9 mmoles), 3-chloroaniline (1.78 g, 13.9 mmoles), an anhydrous *p*-toluene-sulfonic acid (from 2.64 g (13.9 mmoles) of the monohydrate, dried by azeotropic distillation) in benzene (50 ml) was refluxed 15 hours under nitrogen. The cooled reaction mixture was diluted with dichloromethane and the solution was washed with 1*M* sodium bicarbonate and

with water. The solution was dried, filtered, and concentrated. Trituration of the residue with carbon tetrachloride induced crystallization, furnishing **16.2** (2.23 g, 37%), as yellow crystals, mp 182-184° from ethyl acetate; ir: 3050 (NH), 1610 (CO), 1590, 1550, 1520, 1230, 1160; ¹H nmr (deuteriochloroform, perdeuteriodimethyl sulfoxide): 12.50 (br s, 1H, N*H*), 7.36 (s, 5H, *Ar*), 7.30-7.00 (m, 4H, *Ar*), 5.62 (s, 2H, -C*H*₂C₆H₅), 4.38 (t, *J* = 3 Hz, 2H, -C*H*₂-), 4.10 (t, *J* = 3 Hz, 2H, -C*H*₂); ms: 432 (7, M⁺ for ³⁷Cl), 430 (10, M⁺ for ³⁵Cl), 91 (100, [C₇H₇]⁺).

Anal. Calcd. for C₂₀H₁₆Cl₂N₄OS: C, 55.69; H, 3.74; Cl, 16.44; N, 12.99; S, 7.43. Found: C, 55.61; H, 3.80; Cl, 16.26; N, 12.71; S, 7.44.

5,7-Dihydro-3-(phenylmethyl)thieno[3',4'-5,6]pyrano[2,3-*d*]-1,2,3-triazol-8(3*H*)-one (15).

Formed in addition to **14.1**, compound **15** (1.01 g, 28% yield (corrected), mp 210-212° from acetonitrile) was eluted from silica gel as described for **14.1**; ir: 3050, 1680 (CO), 1640, 1570, 1540, 1440, 1420, 1340, 1180, 1100; uv 215 (3.27), 253 (3.62); ¹H nmr (deuteriochloroform, perdeuteriodimethyl sulfoxide): 7.40 (s, 5H, *Ar*), 5.69 (s, 2H, -C*H*₂C₆H₅), 4.29 (t, *J* = 4.5 Hz, 2H, -C*H*₂-), 3.95 (t, *J* = 4.5 Hz, 2H, -C*H*₂-); ¹³C nmr: (400 MHz) 171 (CO), 161 (C(4a)), 153 (C(3a)), 134 (C(1')), 131 (C(8a)), 130.3 (C(3')), 130.2 (C(4')), 129 (C(2')), 125 (C(7a)), 52 (-C*H*₂C₆H₅), 36 (C(5)), 31.5 (C(7)); ms: 285 (9, M⁺), 256 (29), 91 (100, [C₇H₇]⁺).

Anal. Calcd. for C₁₄H₁₁N₃O₂S: C, 58.93; H, 3.88; N, 14.73; S, 11.24. Found: C, 58.98; H, 3.71; N, 14.68; S, 11.26.

According to SINEPT experiments [7], the *H*(7) resonance (δ 3.95 ppm) coupled to the carbonyl (δ 171 ppm), C(4a) (δ 161), and C(7a) (δ 125) resonances. Also, the *H*(5) resonance (δ 4.3 ppm) coupled to the C(4a) (δ 161) and C (7a) (δ 125) resonances. Irradiation of the benzyl methylene proton resonance (δ 5.7) showed that it coupled to C(3a) (δ 153), C(1') (δ 134), and to C(2') (δ 129).

5,6-Dihydro-3-(phenylmethyl)thieno[2',3';5,6]pyrano[2,3-*d*]-1,2,3-triazol-8(3*H*)-one (16).

A mixture of **11** (3.21 g, 10.0 mmoles), aniline (0.93 g, 10.0 moles), and potassium *t*-butoxide (1.7 g, 15 mmoles) in *t*-butyl alcohol (120 ml) was refluxed 5 hours. The mixture was concentrated and the residue was partitioned between dichloromethane and water. The organic solution was washed with water, 1*N* hydrochloric acid, and with water; the solution was dried, filtered, and concentrated. The residue was a mixture of **16** and a minor byproduct **17**, which were separated by chromatography over silica gel. Dichloromethane-ethyl acetate (98:2 by volume) eluted **16** (1.25 g, 44%) as the more mobile component, and it crystallized from acetonitrile - petroleum ether as colorless crystals, mp 157-160°; ir: 3050, 2950, 1680 (CO), 1660, 1570, 1530, 1420, 1350, 1180, 1100, 1060, 1020, 870, 800; uv: 234 (4.20), 327 (3.53); ¹H nmr 7.40 (s, 5H, *Ar*), 5.60 (s, 2H, -C*H*₂C₆H₅), 3.42 (s, 4H, 2 - C*H*₂-); ms: 286 (4, [M + 1]⁺), 285 (23, M⁺), 91 (100, [C₇H₇]⁺).

Anal. Calcd. for C₁₄H₁₁N₃O₂S: C, 58.93; H, 3.88; N, 14.73; S, 11.24. Found: C, 58.96; H, 3.79; N, 14.82; S, 11.50.

3-[[2-[5-Chloro-1-(phenylmethyl)-1*H*-1,2,3-triazol-4-yl]-2-oxoethyl]thio]-*N*-phenylpropanamide (17).

Compound **17** was isolated by silica gel chromatography as described for **16** and was eluted after the latter. Compound **17** (0.3 g, 7%) crystallized from dichloromethane-petroleum ether as cream-colored crystals, mp 124-125°; ir: 3420, 1690 (-COCH₂-), 1600 (-CONHPh), 1520, 1500, 1460, 1320, 1250, 1010; ¹H nmr: 7.90 (s, 1H, N*H*), 7.57-7.03 (d, (2H), m (7H), t (1H), 2 C₆H₅-), 5.50

(s, 2H, -CH_2C$_6$H$_5$), 3.98 (s, 2H, -COCH_2S-), 2.93 (t, J = 6 Hz, 2H, -CH_2-), 2.65 (t, J = 6 Hz, 2H, -CH_2-); ^{13}C nmr: 188 (-COCH$_2$S-), 169 (-CONHPH), 140, 138, 133, 129.4, 129.2 (arom -CH-), 129.1 (arom -CH-), 128.9 (arom -CH-), 128.9 (arom -CH-), 128.1 (arom -CH-), 124 (arom -CH-), 119 (arom -CH-), 52 (-CCH$_2$Ph), 38 (-CH$_2$-), 37 (-CH$_2$-), 29 (-CH$_2$-); ms: 416 (3, M$^+$ for ^{37}Cl). 414 (7, M$^+$ for ^{35}Cl), 378 (9, [M - HCl]$^+$), 91 (100, [C$_7$H$_7$]$^+$).

Anal. Calcd. for C$_{20}$H$_{19}$ClN$_4$O$_2$S: C, 57.89; H, 4.61; Cl, 8.54; N, 13.50; S, 7.73. Found: C, 57.72; H, 4.66; Cl, 8.49; N, 13.44; S, 8.02.

8-Phenyl-1,5,7,8-tetrahydro-1-(phenylmethyl)-4H-thieno[3,4-*e*]-1,2,3-triazolo[4,5-*b*]pyridin-4-one (18.1).

Formed in addition to **19.1**, compound **18.1** was isolated by silica gel chromatography as described for **19.1**, and was eluted after the latter. Compound **18.1** (1.61 g, 53%), mp 277-280°, crystallized from ether-dichloromethane; ir: 1680 (CO), 1640, 1570, 1540, 1440, 1420, 1340, 1180; uv: 227 (4.08), 291 (4.12); ^{1}H nmr: 7.61-7.40 (m, 5H, *Ar*), 7.28-7.05 (m, 3H, *Ar*), 6.50-6.40 (m, 2H, H(2') and H(6')), 5.15 (s, 2H, -CH$_2$C$_6$H$_5$), 4.27 (t, J = 3 Hz, 2H, H(5)), 3.77 (t, J = 3 Hz, 2H, H(7)); ms: 361 (5, [M + 1]$^+$), 360 (20, M$^+$), 359 (16, [M - 1]$^+$), 331 (27), 241 (22), 91 (100, [C$_7$H$_7$]$^+$).

Anal. Calcd. for C$_{20}$H$_{16}$N$_4$OS: C, 66.64; H, 4.47; N, 15.54; S, 8.89. Found: C, 66.36; H, 4.33; N, 15.58; S, 9.15.

8-(3-Chlorophenyl)-1,5,7,8-tetrahydro-1-(phenylmethyl)-4H-thieno-[3,4-*e*]-1,2,3-triazolo[4,5-*b*]pyridin-4-one (18.2).

Formed in addition to **19.2**, compound **18.2** was isolated by silica gel chromatography as described for **19.2**, and was eluted after the latter. Compound **18.2** (0.5 g, 27%) crystallized from dichloromethane as colorless crystals, mp 286-289°; ir: 1640 (CO), 1590, 1560, 1480; uv 247 (4.06), 286 (4.09); ^{1}H nmr (deuteriochloroform, perdeuteriodimethyl sulfoxide): 7.67-7.20 (m, 7H, *Ar*), 6.65-6.40 (m, 2H, H(2') and H(6')), 5.26 and 5.01 (AB q, J_{AB} = 16.5 Hz, 2H, -CH$_2$C$_6$H$_5$), 4.13 (br s, 2H, H(5)), 3.77 (br s, 2H, H(7)); ms: 396 (3, M$^+$ for ^{37}Cl), 3.94 (6, M$^+$ for ^{35}Cl), 365 (18), 91 (100, [C$_7$H$_7$]$^+$).

Anal. Calcd. for C$_{20}$H$_{15}$ClN$_4$OS: C, 60.83; H, 3.83; Cl, 8.98; N, 14.19; S, 8.12. Found: C, 60.96; H, 3.82; Cl, 8.88; N, 14.20; S, 8.03.

8-Phenyl-1,8-dihydro-1-(phenylmethyl)-4H-thieno[3,4-*e*]-1,2,3-triazolo[4,5-*b*]-4-one (19.1).

A mixture of **14.1** (3.33 g, 8.39 mmoles) and potassium *t*-butoxide (1.45 g, 12.9 mmoles) in *t*-butyl alcohol (200 ml) was stirred under nitrogen at 25° for 68 hours. The mixture was concentrated, and the residue was partitioned between water and dichloromethane. The organic solution was dried, filtered, and concentrated. The crude product was a mixture of two major components, **18.1** and **19.1**, which were separated by chromatography over silica gel. Dichloromethane-ethyl acetate (7:3 by volume) eluted **19.1** first. It crystallized from ether-dichloromethane to give a pure sample (0.64 g, 21%), as cream-colored crystals, mp 224-225°; ir: 1660 (CO), 1580, 1550, 1510, 1350, 1290, 1190, 1150, 870; uv 251 (4.40), 281 (4.02); ^{1}H nmr (deuteriochloroform, perdeuteriodimethyl sulfoxide): 8.45 (d, J = 3 Hz, 1H, H(5)), 7.70-7.13 (m, 8H, *Ar*), 6.64-6.48 (m, 2H, H(2') and H(6')), 6.32 (d, J = 3 Hz, 1H, H(7)), 5.13 (s, 2H, -CH$_2$C$_6$H$_5$); ms: 359 (6, [M + 1]$^+$), 358 (21, M$^+$), 357 (23, [M - 1]$^+$), 329 (50), 253 (13, [M - C$_7$H$_7$N]$^+$), 239 (11, [M - C$_7$H$_7$N$_2$]$^+$), 91 (100, [C$_7$H$_7$]$^+$).

Anal. Calcd. for C$_{20}$H$_{14}$N$_4$OS: C, 67.02; H, 3.94; N, 15.63; S, 8.95. Found: C, 66.90; H, 3.84; N, 15.80; S, 8.97.

8-(3-Chlorophenyl)-1,8-dihydro-1-(phenylmethyl)-4H-thieno[3,4-*e*]-1,2,3-triazolo[4,5-*b*]pyridin-4-one (19.2).

A mixture of **14.2** (2.00 g, 4.64 mmoles) and potassium *t*-butoxide (0.800 g, 7.13 mmoles) in *t*-butyl alcohol (120 ml) was stirred under nitrogen for 20 hours at 25° and for 1 hour in a 90° oil bath. The mixture was concentrated, and the residue was partitioned between water and dichloromethane. The organic solution was dried, filtered, and concentrated; and the residue, which contained two major products (**18.2** and **19.2**), was chromatographed over silca gel. Dichloromethane-ethyl acetate (4:1 by volume) eluted compound **19.2** (0.51 g 28%) as the more mobile product. It crystallized from dichloromethane-ethyl acetate as cream-colored crystals, mp 259-260°; ir: 1650 (CO), 1580, 1500; uv: 222 (3.64), 255 (3.94), 279 (3.64), 350 (3.51); ^{1}H nmr: 8.40 (d, J = 4.5 Hz, 1H, H(5)), 7.67-7.10 (m, 7H, *Ar*), 6.65-6.48 (m, 2H, H (2') and H(6')), 6.21 (d, J = 4.5 Hz, 1H, H(7)), 5.30 (s, 2H, -CH$_2$C$_6$H$_5$); ^{13}C nmr (400 MHz, deuteriochloroform and perdeuteriodimethyl sulfoxide): 168.6 (*CO*), 143.7 (*C*(7a)), 143.1 (*C*(8a)), 138.5 (*Ar*), 136 (*Ar*), 135.5 (*Ar*), 133 (*C*(4a)), 132.6 (*C*(3a)), 132.3 (*Ar*), 131.6 (*Ar*), 130.4 (*Ar*), 129.5 (*Ar*), 128.9 (*C*(5)), 128.8 (*Ar*), 128.5 (*Ar*), 126.4 (*Ar*), 106.3 (*C*(7)), 53 (-CH$_2$C$_6$H$_5$); ms: 394 (6, M$^+$ for ^{37}Cl), 392 (17, M$^+$ for ^{35}Cl), 363 (65), 91 (100, [C$_7$H$_7$]$^+$).

Anal. Calcd. for C$_{20}$H$_{13}$ClN$_4$OS: C, 61.14; H, 3.33; Cl, 9.08; N, 14.26; S, 8.16. Found: C, 61.50; H, 3.51; Cl, 8.78; N, 14.20; S, 7.99.

According to SINEPT experiments [7], the H(5) resonance (δ 8.4 ppm) coupled to the carbonyl (δ 168.6 ppm), *C*(7a) (δ 143.7), *C* (4a) (δ 133), and to *C*(7) (δ 106.3). Also, irradiation of H(7) (δ 6.21) showed that it coupled to *C*(7a) (δ 143.7), *C*(4a) (δ 133), and to *C*(5) (δ 128.9).

Acknowledgment.

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[5] H(2') and (6') were magnetically equivalent in **8.4** and **8.5**. In each compound the two protons resonated as a single doublet.

[6] The perhaps unlikely regioisomer **20** might have arisen indirectly from **4.1**. Conceivably, formation of **20** would have begun with attack of enamine on *C*(5) of **4.1**. Rearrangement of the resulting acid chloride-enamine followed by transamination and ring-closure would have produced **20**.

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